

# **EXHIBIT 38**



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**Target Audience** Neurologists, family physicians, general practitioners, internal medicine specialists, rheumatologists, physical medicine and rehabilitation specialists, osteopathic medicine specialists, and other physicians and healthcare professionals who treat patients with pain

**Learning Objectives** After reading this newsletter participants should be able to:

- Understand how to best utilize the multiple pharmacologic drug delivery and release systems for both opioid and non-opioid analgesics to manage chronic pain
- Recognize that chronic pain is a disease that is diagnosable and treatable
- Distinguish between neuropathic and other types of pain
- Develop and implement pain management plans that address the specific needs of individual patients
- Identify the means to balance the risk and benefits associated with opioid analgesic therapy for chronic pain

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Dr King has indicated that he is a member of the speakers bureau for Eli Lilly, Pfizer Inc, and Sanofi-Aventis.

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## New Delivery Systems in Pain Management



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Dr Nicholson has indicated that he is a research consultant for Pfizer, is a retained consultant for Alpharma, and is a member of the speakers bureau for King Pharmaceuticals.

Current treatment for individuals with moderate to severe chronic pain frequently requires combination therapy. Multiple drug therapy may be delivered through various routes in order to minimize side effects and maximize efficacy. The patient with long-standing chronic pain due to neuropathic and/or non-neuropathic pathophysiology may also manifest comorbid complications including sleep disorders, depression, and anxiety, as well as various other psychosocial problems. Therefore, to successfully treat a person with chronic pain, the clinician must utilize a whole-person chronic disease state model.

### Proper Diagnosis Is Essential

Effective management of chronic pain

begins with an appropriate diagnosis of the type of pain. Chronic pain may relate to an underlying disease process; for example, a patient with diabetes may develop burning pain accompanied by numbness in a stocking distribution that worsens at rest. Not infrequently, the initial neurologic examination may reveal only subtle sensory changes to vibration, cold, and monofilament testing. This diagnosis may contrast greatly with a patient who presents with severe disabling neuropathic pain secondary to an episode of shingles that results in injury to the peripheral and central nervous systems. This neuropathic pain condition, known as postherpetic neuralgia, often

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## Chronic Pain Is a Disease



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For the primary care physician (PCP), the assessment and management of patients with pain may be one of the most challenging areas of practice. A successful approach includes identifying the underlying etiology of the pain, establishing a diagnosis, defining a course of treatment, and monitoring improvement, although it is often not easily accomplished. This is especially true for chronic pain syndromes, many aspects of which are not appreciated or understood.<sup>1,2</sup>

### What is the Cause?

In acute pain, the cause (eg, trauma) is generally known, the duration is short and well characterized, and the treatment is aimed at resolving the underlying cause and supporting the patient through the painful period (which is usually self-limited) with medication and short-term rehabilitation. In chronic pain, however, the cause may be unknown. Even if a cause (eg, postherpetic neuralgia) is identified, pain persists after apparent healing. Most importantly, the underlying cause of chronic pain may be the pain disorder itself, in which case the desired outcomes are controlling pain—not "curing" it—and maximizing function and quality of life.

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**EDITOR'S PERSPECTIVE**

# The Growing Problem of Neuropathic Pain

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**A**lthough all chronic pain conditions can be difficult to manage, neuropathic pain is among the most challenging.

Neuropathic pain is not a new problem. Complex regional pain syndrome (CRPS), discussed in Dr Argoff's article on page 5, was first described during the Civil War. However, many—if not most—cases of this disorder still appear to go undiagnosed and the syndrome's prevalence remains unclear. Over the years, multiple treatments have been introduced, most with an initial enthusiasm that subsequently turned to disappointment. Treatments such as sympathectomies and Bier blocks have fallen by the wayside. Even spinal cord stimulators, which appear to have the potential to provide relief, were recently reported to provide little long-term benefit for CRPS. As of yet, no medication has been FDA-approved for its treatment.

Several factors indicate that neuropathic pain will continue to be a growing problem. We are in the midst of what has been described as "an epidemic of diabetes mellitus." As the baby-boom generation enters the geriatric stage, we can expect to see a rise in neuropathic pain disorders associated with Parkinson's disease and stroke. Although the recent introduction of a vaccine for shingles should have a significant impact on the number of cases of

postherpetic neuralgia (PHN), the vaccine reduces the rate of PHN by only two thirds, leaving tens of thousands of patients at risk for developing this painful disorder.

Numerous medications have been tried in treating neuropathic pain, and new agents and drug-delivery systems continue to be introduced for pain management, as Dr Nicholson elaborates on page 1, but only five are currently FDA-approved for neuropathic pain conditions. It is interesting to note that of this group, three—carbamazepine, gabapentin, and duloxetine—were initially approved for the treatment of seizures or depression and one—pregabalin—was simultaneously approved as an analgesic and an anticonvulsant. The lidocaine patch 5% is the only drug approved solely for the treatment of a neuropathic pain disorder.

Other articles in this issue highlight the current state of our knowledge regarding pain management (see *Chronic Pain Is a Disease* by Dr Rosenthal on page 1) and the ongoing efforts to improve treatment—see *The 10-Minute Office Visit: How to Evaluate Pain Treatment Success/Failure* by Dr McCarberg on page 3 and Dr Cole's article on page 7 discussing the *Parameters Involved in Initiating Opioid Therapy for Chronic Pain*. ☞

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**ABOUT THE NIPC**

The National Initiative on Pain Control® (NIPC®) is an integrated CME education initiative that was established in 2001 to help physicians improve outcomes for their patients who have pain.

Living with pain has deleterious effects on many aspects of the patient's life including deterioration of physical functioning, the development of psychological distress and psychiatric disorders, and impairment of interpersonal functioning. Of special concern, less than optimal training of physicians in pain disorders has led to the underassessment and undertreatment of patients who are living with pain. The program heightens physician awareness of the impact of pain on the patient's daily living in terms of quality of life, lost workdays, and societal/familial consequences.

NIPC addresses the barriers to achieving pain control by providing potential pathways for action and expected amelioration of their patients' pain. By providing physicians with the latest advances and strategies in pain management, they will be better able to translate clinical data into clinical practice.

All NIPC programs are developed and continuously evaluated by the NIPC Education Council, an expert, multidisciplinary team of specialists, researchers, and practicing physicians in pain management. The NIPC Faculty includes nationally respected experts in the pain management field.

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## THE 10-MINUTE OFFICE VISIT

# How to Evaluate Pain Treatment Success/Failure



**Bill H. McCarberg, MD**, Founder, Chronic Pain Management Program, Kaiser Permanente San Diego, Assistant Clinical Professor (Voluntary), University of California, San Diego, San Diego, California

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Ten minutes is not enough time to evaluate any complex problem whether it is diabetes, chronic obstructive pulmonary disease, congestive heart failure, or chronic pain. The physical examination and questions that need to be asked will take more than 10 minutes. In addition, many patients in the primary care setting return for a visit with a list of problems needing time and attention. But the reality is that the primary care physician (PCP) does not have enough time yet still has to address the patient's concerns. Every PCP develops a method to make the visit more efficient. Following are several suggestions to make the visit less stressful for the PCP and less rushed for the patient.

### Forms and Questionnaires

To make the follow-up evaluation more focused and effective, handouts and questionnaires can be used. At the initial visit, give the patient a form that includes a pain scale, a description of functionality, a list of possible side effects of pain medications, and a section for the patient to list previous treatments for pain. This handout will direct the follow-up visit regarding the important outcome variables of pain and function. Without this focus, the visit can become longer without documenting the outcome you need:

"Hello Mrs Smith, how are you today?"

*"Not so good doctor, I'm still not sleeping and I was so constipated I had to stop those pills you gave me."*

Since the initial visit, the patient may have had reduced pain, worked in the garden, and attended a social function with her husband, but she is now complaining about her sleep and a side effect of the treatment. The entire visit may then revolve around the constipation

and sleep issues and ignore the progress in pain control and functionality that has been gained. With the questionnaire available at the visit, the result can be different:

"Hello Mrs Smith, I see your pain has gone from 8 down to 5 and you planted those tomatoes you talked about during the last visit."

*"Yes, doctor, I am doing better but my sleep did not improve and I was so constipated I had to stop those pills you gave me."*

The patient's behavior and complaint are the same, but the focus now is on how to maintain the progress, treat the side effects, and improve sleep. A 10-minute visit can concentrate on the improvements as well as deal with her concerns.

Handouts may be difficult for your practice or the patient may forget to bring the form back. In this case, have the receptionist give out the questionnaires at check-in for the patient to fill out while waiting for the appointment. There are many available resources that measure pain and function. Examples of these resources can be downloaded from the NIPC Web site at [www.PainKnowledge.org](http://www.PainKnowledge.org) for use in your practice.

### The 4 A's Model

Many practices are not designed to accommodate questionnaires. The flow of patients, cramped facilities, and sheer volume of potential forms for multiple conditions make the use of handouts unrealistic. What strategy can you use when forms are not practical?

Having a method of follow-up facilitates the information you need and keeps the patient focused on the important outcomes. My patients are so accustomed to being asked about pain that they readily report scores and how the current pain level relates to past experiences. A pain

diary would be more accurate but not possible in many practices.

Similarly, in a short office visit it may seem difficult to evaluate treatment success in a patient with diabetes. Most diabetics are taking multiple drugs, often 10 or more, and during each visit the PCP must evaluate the patient's hypertension and cholesterol treatments, perform neurologic and retinal examinations, and address diet, exercise, sleep, and psychosocial issues. The PCP is able to accomplish this quickly since the outcome variables are well defined: home glucose monitoring, hemoglobin and microalbumin screening, and monofilament and fundoscopic examinations.

With the correct preparation the patient with chronic pain can be evaluated for treatment success in a short office visit. Passik and Weinreb have devised the 4 A's Model as a method to focus you and your patient on the important outcomes of pain management and functionality:

**Analgesia.** Multiple scales, including verbal and multilanguage scales, are available, and much emphasis has been placed on recording pain scores. It is

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### Essential Patient Questions/Topics for Each Office Visit

- What is your pain rating (0-10 scale) most days? At its worst? At its best?
- What percentage of pain relief have you experienced (0%-100%)?
- Have you increased your functionality on this treatment plan?
- Has this treatment plan increased your quality of life?
- Are you experiencing any side effects from your current medications?
- Have you experienced any anxiety, depression, or sleep problems?
- Discuss any aberrant behaviors in an open and straightforward manner.



## New Delivery Systems

CONTINUED FROM PAGE 1

presents with a combination of spontaneous pain symptoms described as shooting, electric shock-like, and burning in character. In addition, signs of evoked pain may include allodynia (a painful response to a non-painful stimulus) to touch, cold, and/or heat. Therefore, a patient's underlying disease and a description of the characteristics and distribution of pain will often provide valuable leads for making the proper diagnosis.<sup>1</sup>

Patients with chronic pain frequently present not only with neuropathic pain but also with a component of non-neuropathic pain. This often is the case with chronic low back pain secondary to causes such as inflammatory degenerative joint disease and disc disease that is accompanied by a neuropathic component involving the spinal nerve roots. Effective management requires that a clinician evaluate the patient and understand which medical treatments will provide optimal results.<sup>2</sup>

### Tailor the Treatment Plan

Treatment options can be individualized based on the type, characteristics, and intensity of pain. Administration of medications based on pain intensity may determine, for example, whether to begin with only a topical medication for mild to moderate pain, or with a combination of topical and oral therapies for moderate to severe pain. A recent study that examined the role of sodium and

calcium channels in inflammatory and neuropathic pain suggests that medications that target mechanisms (ie, ion channel receptors) may be effective for treating these conditions.<sup>3</sup>

Currently available delivery systems for the topical administration of drugs that block sodium channel activity include lidocaine preparations, which are applied several times a day and may be combined with capsaicin or other local anesthetics. Lidocaine may also be imbedded in a unique matrix formulation that allows a continuous slow release of the drug. It is important to distinguish between the dermal delivery system of the lidocaine patch 5%, which will not result in systemic levels of lidocaine when applied as directed, and several of the topical creams that penetrate the subdermal layer and result in systemic uptake. The acceptance rate of the lidocaine patch formulation in patients with allodynia is excellent and the side-effect profile is minimal. Current therapeutic uses may include treatment of allodynia related to nerve injury (ie, postherpetic neuralgia, for which it is indicated), as well as treatment of back pain (acute and chronic)\* and knee pain related to osteoarthritis.<sup>4</sup> In addition to the lidocaine patch, there are four other agents indicated for the treatment of various neuropathic pain conditions (see Table; see also proposed evidence-based neuropathic pain treatment algorithm, page 13).

Optimal management of most chronic pain—whether inflammatory, neuropathic, or mixed—will require the addition of an oral or transdermal medication. Current technology includes immediate-release and sustained-release formulations of opioids that are indicated for the treatment of moderate to severe acute and chronic pain, including neuropathic pain.<sup>5</sup> The thoughtful decision to utilize opioid therapy must be based on the individual patient and should include a careful assessment of risks and benefits.<sup>6</sup> Numerous guidelines and Web sites, such as the official site of the National Initiative on Pain Control® at [www.PainKnowledge.org](http://www.PainKnowledge.org), are available to assist the clinician in the management of patients who are appropriate candidates for opiate therapy.

\*Not FDA approved for this use.

Recently, a 24-hour extended-release formulation of tramadol was approved for the treatment of moderate to moderately severe pain. The slow-release mechanism, which allows for once-daily dosing, demonstrated significant pain relief as compared with placebo over the duration of a 12-week study.<sup>7</sup> The dual mechanisms of tramadol—mu-receptor activation (M1 metabolite six times the potency of tramadol) and reuptake inhibition of norepinephrine and serotonin—are likely to have a significant role in efficacy for both inflammatory and neuropathic pain.

Sustained-release oral opiate compounds are currently available in imbedded matrix formulations (eg, oxycodone, morphine) and polymer-coated sphere technology (morphine). Oxymorphone ER (recently approved for treating moderate to severe pain), a semi-synthetic opiate and metabolite of morphine, is being evaluated for treating moderate to severe chronic back and osteoarthritis pain. In a recent clinical trial comparing oxymorphone extended release with oxycodone controlled release and placebo in the treatment of patients with chronic low back pain, oxymorphone was shown to be equianalgesic to oxycodone at half the milligram daily dosage with a comparable safety profile.<sup>8</sup> Remoxy™, a 12-hour oxycodone preparation in a tamper-resistant formulation, is undergoing analgesia and abuse deterrent trials.<sup>9</sup> Advantages of the sustained-release formulations include improved analgesia profiles over 24 hours, compliance, and decreased side-effect profiles due to less fluctuation in plasma drug levels.

Recent studies have demonstrated high levels of satisfaction with the use of 24-hour sustained-release morphine in a spherical preparation for the treatment of moderate to severe chronic and neuropathic pain.<sup>10</sup> Oral preparations of opiates allow for rapid titration and individualization of dosing predicated on the pain pattern and intensity. However, side effects, particularly constipation, may be somewhat higher when opiates are given by mouth.<sup>11</sup>

Transdermal technology is best utilized when the clinician desires to obtain systemic absorption and distribution of a

### FDA-Approved Treatments for Neuropathic Pain

- Carbamazepine
  - trigeminal neuralgia
- Duloxetine
  - peripheral diabetic neuropathy
- Gabapentin
  - postherpetic neuralgia
- Lidocaine Patch 5%
  - postherpetic neuralgia
- Pregabalin
  - peripheral diabetic neuropathy
  - postherpetic neuralgia

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## DECODING COMPLEX REGIONAL PAIN SYNDROME

# How Would You Treat These Patients?



**Charles E. Argoff, MD**, Assistant Professor of Neurology, New York University School of Medicine, New York, New York; Director, Cohn Pain Management Center, North Shore University Hospital, Manhasset, New York

*Dr Argoff has indicated that he receives grant/research support from UCB Pharma and Cephalon; is a retained consultant for Allergan, Endo Pharmaceuticals, and Pfizer Inc; and is a member of the speakers bureau for Pfizer Inc.*

**C**omplex regional pain syndrome (CRPS) is one of the most difficult conditions to treat. Due to the undefined pathophysiology of CRPS, physicians must rely on clinical presentation and the use of diagnostic tools to determine an appropriate diagnosis and treatment recommendations. Tables 1 and 2 include some of the common clinical characteristics and measurements that are used to confirm diagnosis of CRPS.

Patients can present with one of two types of CRPS: type I (previously referred to as "reflex sympathetic dystrophy" or RSD), which is preceded by minor injuries or fracture of a limb, or type II (previously referred to as "causalgia"), which occurs following injury to a major peripheral nerve.<sup>1</sup>

CRPS occurs most commonly in women between the ages of 36 to 46 years, and while the characteristic burning, pricking, or shooting pain sensations can be found in several parts of the body, they typically present in the upper or lower extremities, especially the hand or foot.<sup>1,2</sup>

Although these two syndromes may appear similar in clinical presentation, they differ with respect to the demonstration of a major nerve lesion in type II and the absence of such injury in type I. Further information regarding the diagnostic criteria of each can be found in Table 1.

**Following are brief descriptions of patients who present with each of these conditions. Review the**

**information and consider how YOU would treat these patients.**

### Patient With CRPS Type I

The patient is a 50-year-old woman who, because of persistent right upper extremity pain following a cervical laminectomy, underwent a cervical epidural steroid injection. Immediately following the injection, the patient complained of severe burning pain, swelling, and allodynia in the right upper extremity. No other cause was found for this reaction and all diagnostic tests, including magnetic resonance imaging bone scan and electromyography (EMG)/nerve conduction velocity (NCV), were negative. The patient tried physical therapy, which proved to be unsuccessful and provided no relief.

1. Taking into consideration the patient's complaints, test results, and the unresponsiveness to physical therapy alone, what would you do next? (Select all that apply)
  - A. Pharmacological intervention
  - B. Sympathetic nerve blocks
  - C. Physical therapy in combination with other medical/interventional therapies
  - D. Cognitive-behavioral treatment
  - E. All of the above
2. The patient also has previously tried gabapentin,\* pregabalin,\* duloxetine,\* topical lidocaine,\* oral steroids,\* and amitriptyline\* without significant benefit or side effects. She notes that the only treatment that seemed to alleviate the pain was oxycodone, which was also well tolerated, but she would like to be more comfortable. She asks you for other medication treatment suggestions. What is your recommendation?
  - A. Apologize and tell her that nothing more can be done
  - B. Suggest the use of ibuprofen
  - C. Prescribe lamotrigine\* beginning at 25 mg/day with the plan to titrate higher
  - D. Suggest the use of an opioid regimen
  - E. C or D

\* Not FDA-approved for this use.

**Table 1. Diagnostic Criteria for Complex Regional Pain Syndrome (CRPS)**

#### CRPS Type I (reflex sympathetic dystrophy [RSD])

1. The presence of an initiating noxious event or a cause of immobilization
2. Continuing pain, allodynia,\* or hyperalgesia\* with which the pain is disproportionate to the inciting event
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor (sweat gland) activity in the painful region
4. The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

NOTE: Criteria 2, 3, and 4 are necessary for a diagnosis of CRPS (criteria 1 is not always present).

#### CRPS Type II (causalgia)

1. Continuing pain, allodynia,\* or hyperalgesia\* after a nerve injury, not necessarily limited to the distribution of the injured nerve
2. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain
3. The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction

\*allodynia = pain from a stimulus that does not normally evoke pain

hyperalgesia = an exaggerated response to a normally painful stimulus

Merskey H, Boduk N. *Classification of Chronic Pain*. 2nd ed. Seattle, WA: IASP Press; 1994.

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## Chronic Pain Is a Disease

CONTINUED FROM PAGE 1

Understanding that chronic pain is a disease is key to successfully managing patients who present with it. Chronic pain is frequently the result of pathologic changes in nerve function and physiology, known as neuropathic pain. This point highlights the fact that chronic pain often results from an underlying disorder that causes increased sensitization to pain at both the peripheral and central levels. Patients with neuropathic pain may present with evidence of increased sensitization, with symptoms such as allodynia (pain from a stimulus that does not normally evoke pain) or hyperalgesia (an exaggerated response to a normally painful stimulus).<sup>1,3,4</sup>

In the case of chronic neuropathic pain, the etiology to be identified is disturbance of nerve function (eg, neuropathy or neuralgia), and the diagnosis is "pain." While it is important to rule out other possible causes of chronic pain, it is also critically important to recognize that nerve pathophysiology causes the pain and that patient concerns and limitations are, therefore, neither imagined nor fabricated.

### Quality of Life

Chronic pain as a disease entity has not been fully appreciated, and there is a high prevalence of untreated or undertreated pain. Furthermore, there are far-reaching consequences of chronic pain, which may include psychological morbidity, socioeconomic effects, social difficulties, and decreased quality of life.<sup>1,2</sup>

The emphasis for managing a patient with chronic pain, therefore, is improving the clinical outcomes of functionality and quality of life. Although reducing the level of chronic pain is an important aspect of treatment, ameliorating or curing pain should not be expected, and development of a comprehensive treatment plan is most appropriate.

In general, the PCP is trained and experienced in using a broad-based, biopsychosocial approach to patient care in medical practice. Yet, in the context of

chronic pain, there is often a tendency to lose sight of that approach and to focus on the pain, prescribe medication, and expect pain alleviation as the primary outcome. If treatment goals can be modified to include the improvement of patient well-being as well as the expectation of some level of pain, PCPs can use their skills to be highly successful in caring for patients with pain.

### Chronic Pain Management

In considering the management of patients with chronic pain, it is helpful to explore analogies with the management of other "non-curable," commonly encountered chronic disease entities such as diabetes or hypertension. For instance, the underlying pathophysiology of diabetes is related to glucose metabolism which, if not controlled over time, may cause significant morbidity that will affect quality of life. While providing medications for blood sugar control is of primary importance, the comprehensive care of a patient with diabetes involves a broader strategy. Interactive goal setting, patient education, exercise, proper diet, weight control, personal monitoring, appropriate referral, and longitudinal follow-up in a doctor-patient relationship support continued adherence to an established plan and identify areas for intervention when the disease is not controlled. In more difficult cases that involve significant

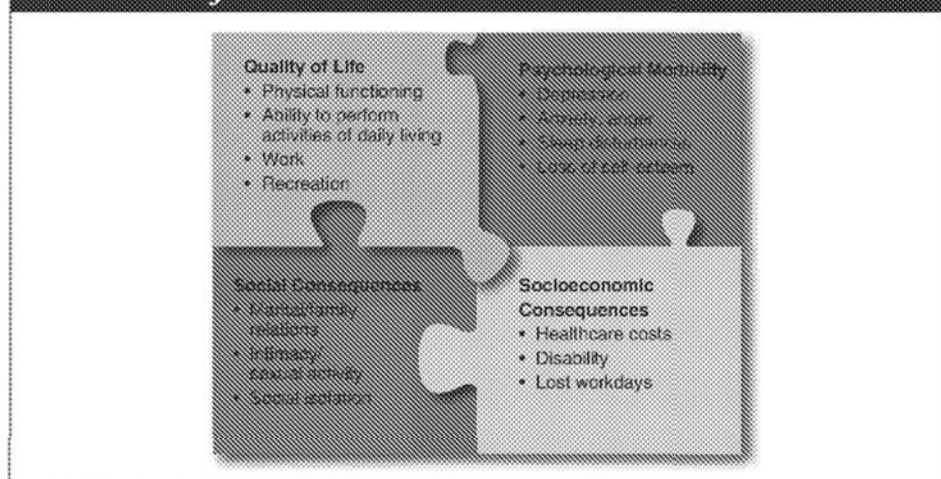
morbidity, other personal, emotional, family, social, and disability issues may need to be assessed and addressed.

Similarly, appropriate treatment plans for patients with chronic pain will involve provision of medication, but many other aspects of care must also be addressed. In fact, the key to a successful plan often lies in getting beyond the emphasis and discussion of pain and medication and working toward the emotional, social, and quality-of-life issues mentioned above.<sup>1,2,5,6</sup> Following are salient points of care to be considered *in addition* to evaluating the pain and the proper medication to treat pain. Supportive discussion and assessment of other areas to address (see Figure 1) include:

**Level of disability and physical functioning** Chronic pain limits function. Once function is limited, patients may not have the capacity to perform in desired ways during work, recreation, or activities of daily living. Loss of function decreases self-esteem and belief in eventual improvement. Therefore, evaluating each patient's functional capacity and the best approach to improving it are critically important. Defining the level of disability and establishing reasonable, achievable short-term goals are needed to help the patient appreciate opportunities for improvement and see results. This allows the physician and patient to

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**Figure 1. Chronic Pain Affects All Aspects of a Patient's Life**





## Special Article on Opioid Therapy

# Parameters Involved in Initiating Opioid Therapy for Chronic Pain



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## Case Study

Mr M. Dillon is a 57-year-old, retired US Marshall with a long history of chronic, persistent pain resulting from a distinguished law enforcement career involving many falls, fights, fractures, and an occasional gunshot or stab wound. He presents with pain in his neck, right shoulder, right sacroiliac joint, lower back, and both hips. His x-rays are normal except for osteoarthritis. Despite soaking in hot baths nightly, frequent massages, and taking several aspirin tablets and shots of whiskey daily, he has not been able to keep his pain intensity score below 5 out of 10 (0 = no pain, 10 = worst pain). Frequently, at night, his pain is excruciating, or 10 out of 10. Over the past week, his pain intensity has been 7 out of 10.

He describes his pain as a mixture of aching, burning, cramping, pulling, stabbing, and throbbing. Furthermore, he notes tingling radiating down the back of his right thigh to his knee. His primary care physician (PCP) has tried "sticking needles in whatever hurts me, stretching me on the 'rack' and giving pain shots when the pain gets too bad." The pain interferes with his dressing (especially putting on and taking off his boots), horseback riding, lifting and bending, household chores, and walking more than short distances. He knows that there are a number of treatments that might be effective, but fears becoming addicted to the "strong stuff." Despite pain complaints, Mr Dillon is in good physical health.

Through a complete clinical workup, Mr Dillon's physician can determine if

opioid therapy is appropriate. Successful administration of opioid therapy can be achieved by following simple, reasonable guidelines and avoiding certain pitfalls (see Table 1).

## Goals of Opioid Therapy

Opioid analgesics are regarded as a first-line therapy for moderate to severe pain.<sup>1,2</sup> As one of the major cornerstones of pain relief, opioids produce analgesia, or pain relief, rather than anesthesia, or the loss of sensation. The primary goals of opioid therapy for Mr Dillon are to reduce pain intensity as well as improve daily function and quality of life.<sup>2</sup> To optimize therapy, Mr Dillon must participate in his own goal setting, helping his physician determine what pain intensity is acceptable, how much functioning is desired, and what degree of side effects is tolerable.

## Patient Assessment and Selection

Proper patient selection for opioid therapy entails a complete medical history and comprehensive physical and psychological examination.<sup>3</sup> In addition to

the office examination, Mr Dillon's evaluation should include laboratory tests to determine hematologic, hepatic, and renal status, as well as to detect the presence of any concomitant conditions. His pain should be evaluated with regard to location, distribution, intensity, timing, and quality, in addition to ameliorating and exacerbating factors. Several self-reported measurement tools have been developed to help quantify pain, including numerical (1 to 10) and categorical (none, little, moderate, severe) scales. Possible pathophysiologic pain mechanisms should also be carefully considered (eg, nociceptive, neuropathic, deafferentation, neuralgia, radiculopathy, central, or psychogenic).<sup>3</sup> Accordingly, Mr Dillon's pain should be classified as either localized or referred, as well as either central, peripheral, or visceral. Diagnostic studies for pain states include x-rays, CT and MRI scans, electromyography, nerve conduction studies, and diagnostic blocks, although in most cases of chronic pain these tests provide limited information. It is also important to obtain medical records from previous practitioners. Once the underlying pain etiology is identified, an appropriate treatment plan can be formulated. It should be noted, however, that it is not always possible to identify the etiology of chronic pain.

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**Table 1. Some Pitfalls in Prescribing Opioids**

- Failure to obtain a history regarding the pain problem
- Failure to perform a physical examination relevant to the pain problem
- Inability or unwillingness to consider or detect substance abuse
- Blindly believing what is claimed without independent confirmation
- Never obtaining medical records from previous practitioners and facilities
- Prescribing opioids without some pain reduction or improvement in function
- Having incomplete or inaccurate medical records
- Being unwilling to use other classes of medication
- Not staying current with published literature regarding opioid therapy
- Not being a member of any professional pain management organization
- Not maintaining good relations with nurses and pharmacists
- Seeing too many patients per day (more than are reasonably seen by other practitioners in the community) and creating high volume practices entirely based upon opioid prescribing



## Special Article on Opioid Therapy

Potential side effects of opioid therapy should be considered in patient selection. As a class, opioids are associated with sedation, mental clouding or confusion, depression, nausea and vomiting, constipation, pruritus, urinary retention, bradycardia, and, rarely, respiratory depression.<sup>1</sup> Opioids should be used with caution in patients with impaired ventilation, bronchial asthma, liver or kidney failure, or increased intracranial pressure. Mr Dillon is in good health without any contraindications to opioid therapy, but continuation of frequent aspirin use and alcohol ingestion might predispose him to gastrointestinal problems. Furthermore, drinking alcohol while taking opioids is not recommended because of additive central nervous system depressant effects.

Patient selection is also important because of the risk of abuse and criminal diversion of opioids. Psychological dependence, or addiction, that leads to overwhelming drug-seeking behavior and compulsive use can occur with opioid therapy, more often with prolonged than short-term administration. Mr Dillon must be screened for use of all substances, both licit and illicit, especially because he has indicated frequent alcohol use. The CAGE, Trauma Screening Test, DAST, or similar screening test should be used to better recognize Mr Dillon's potential for latent or active substance abuse.<sup>4</sup> Furthermore, comprehensive urine drug screening using mass spectroscopy and gas-liquid chromatography (MS/GLC) can identify legal and illegal substances. If more precision is required, serum levels of specific medications can be obtained along with their common metabolites. Mr Dillon's physician should also be vigilant for behavioral patterns that indicate drug abuse in patients, as described by the Drug Enforcement Administration (Table 2).<sup>5</sup> Key to working successfully with Mr Dillon will be his adherence to an agreement that explicitly states the responsibilities of both the patient and the physician, and stipulates the consequences of aberrant opioid use.<sup>6</sup> A substantial amount of research indicates that opioid therapy does not lead to addiction in a majority of patients.<sup>2</sup>

## Patient Education and Communication

Patient education is particularly important when managing long-term, persistent pain and committing to opioid therapy. Mr Dillon should be taught about the role of medications as one part of his overall treatment program and should be encouraged to openly discuss concerns with his physician. The exchange between Mr Dillon and his physician should be matter-of-fact, nonjudgmental, and carried out in the same manner as any discussion about a serious, chronic medical condition. In addition to in-office discussion, Mr Dillon should have access to printed materials about chronic pain, common comorbidities, the role of opioids, monitoring and compliance expected, ground rules for prescribing and renewing prescriptions, and the consequences of violation of the agreement. A number of pharmaceutical companies and device manufacturers have prepared patient education materials, and there are also many resources available on the Internet. However, these may not be fully specific to Mr Dillon's needs. Template electronic medical records allow Mr Dillon's physician to create a base document that can then be personalized. The initial investment of the few

hours to create a personalized document might later save time during clinical contacts. Such a document might also resolve questions potentially raised by regulatory bodies examining opioid therapy in a particular patient.

Mr Dillon should also be informed of the range of options available, as well as the risks and benefits of each treatment. Efficacy limitations and side effects should be clearly discussed. Long-term risks of opioid therapy include endocrine and immune dysfunction, and hyperalgesia, in addition to addiction, physical dependence, and tolerance. Unlike addiction, physical dependence commonly occurs in the clinical setting. Physical dependence is an altered physiological state that necessitates repeated opioid administration to prevent a withdrawal syndrome. Tolerance is a lack of efficacy that develops with continuous opioid administration requiring dose escalation. Regardless of concerns related to psychological and physical dependence, a number of expert groups advocate the judicious use of opioids for chronic pain.<sup>1,2</sup>

The physician's role in patient education is vital to successful administration of opioids for chronic pain. As the prescriber of record for long-term opioid

**Table 2. Common Features of Potential Opioid Abusers\***

- Unusual behavior in the waiting room
- Assertive personality, often demanding immediate action
- Unusual appearance—extremes of either slovenliness or being over-dressed
- Unusual knowledge of controlled substances and/or gives medical history with textbook symptoms, OR gives evasive or vague answers to questions regarding medical history
- Being reluctant or unwilling to provide reference information. Usually has no regular doctor and often no health insurance
- Requests for a specific controlled drug and reluctance to try a different drug
- Fails to keep appointments for further diagnostic tests or refuses to see another practitioner for consultation
- Exaggerates medical problems and/or simulates symptoms
- Exhibits mood disturbances, suicidal thoughts, lack of impulse control, thought disorders, and/or sexual dysfunction
- Has cutaneous signs of drug abuse—skin tracks or “pop” scars on the neck, axilla, forearm, wrist, foot, and ankle

\* Some patients with chronic pain who abuse opioids do not exhibit any of these features.



therapy, Mr Dillon's physician should be able to commit time to patient education and have mid-level practitioner support. Failing to properly assess and manage any patient receiving opioids due to practice demands will put a physician in an indefensible position if challenged regarding opioid treatment.

### Selection of an Initial Opioid Analgesic

Opioids are effective in treating moderate to severe pain not responding to non-opioid analgesics, such as acetaminophen or ibuprofen. Although virtually all types of pain respond to opioid therapy, nociceptive pain, as found with Mr Dillon, is more responsive than neuropathic pain.<sup>1</sup> Depending on analgesic potency, opioids are classified as either strong or weak. Strong opioids include morphine, hydromorphone, meperidine, oxycodone, levorphanol, methadone, and fentanyl. Weak opioids include hydrocodone, codeine, oxycodone, and propoxyphene. In contrast to non-opioid analgesics, opioids have no ceiling effect for efficacy. Upward opioid titration, however, is limited by toxicity. Opioids are metabolized in the liver and excreted by the kidneys.

The World Health Organization still favors the use of morphine as the opioid of choice for Step 3 therapy, but fentanyl, hydromorphone, oxycodone, and oxycodone are commonly used alternatives. Fentanyl, a completely synthetic molecule, may be least likely to create allergic reactions.

Furthermore, current studies suggest that fentanyl may be unlikely to cause delirium,<sup>7,8</sup> although in other research methadone has been shown to have a lower incidence of delirium than fentanyl,<sup>9</sup> and it does not have any known toxic metabolites. Hydromorphone is favored as the opioid of choice among patients with renal insufficiency.<sup>10</sup> Various opioids differ in toxicity, likelihood of histamine-mediated itching and other allergic phenomena, and the potential to interact with other medications through the cytochrome P-450 systems. Hydrocodone and codeine must be converted in the liver to hydromorphone and morphine, respectively, to

achieve pain relief; this conversion does not occur when medications that block 2D6 liver enzyme (eg, selective serotonin reuptake inhibitors, most notably paroxetine and fluoxetine, the serotonin norepinephrine reuptake inhibitor duloxetine, antipsychotics, and antivirals) are also taken.

Opioids are available in both immediate-release and controlled-release formulations. Controlled-release formulations have been developed to deliver the drug into the blood stream at a steady rate, thereby extending the duration of action (for morphine, from 2-4 hours to 12-24 hours) and decreasing frequency of administration (usually to once or twice daily). Controlled-release opioids are appropriate for managing continuous, "background" pain, whereas immediate-release opioids are more applicable for intermittent, "breakthrough" pain (occurring with changes in activity levels or as a result of various treatments). Because of decreased frequency of administration, controlled-release formulations simplify therapeutic regimens and may improve compliance. However, a major disadvantage of controlled-release formulations is cost. One solution may be the use of methadone, an immediate-release formulation of a synthetic opioid with a long half-life, thereby creating relatively stable blood levels. Moreover, controlled-release opioid formulations have received media attention in recent years because of instances of abuse where the controlled-release mechanism was defeated, enabling delivery of large opioid doses. Despite such negative press, opioid therapy has helped millions of Americans with unrelenting chronic pain. Indeed, Mr Dillon might benefit from a controlled-release opioid to establish an optimal level of pain control and an immediate-release opioid to address any breakthrough pain.

### Summary

Opioid analgesics have been demonstrated to be safe and effective through decades of clinical experience and numerous controlled clinical trials. Few physicians will dispute the usefulness of these medications for managing moderate to severe pain. The vast majority of

patients treated with opioids report meaningful improvements in functionality and quality of life. However, prescribers must be mindful of the potential drawbacks of opioid therapy. When practicing in a heavily regulated and scrutinized environment, physicians must adhere to high standards and prescribe responsibly so as not to be exploited by those seeking medication for nonmedical purposes. Although more research is needed to resolve questions about the prolonged use of opioids, many experts support the use of these medications for chronic pain. ✕

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## Decoding CRPS

CONTINUED FROM PAGE 5

**Table 2. Diagnostic Measurements for CRPS**

- Pain assessment
- Skin temperature assessment
- Motor assessment
- Autonomic function assessment

### Patient With CRPS Type II

The patient is a 48-year-old woman who developed a clear right brachial plexus injury and subsequent CRPS type II during plastic surgery treatment for severe burns on her subclavicular and pectoral region. She has limited or no use of her right upper extremity. It is grossly swollen and cold, and

nothing can touch the extremity without resulting in horrific pain. Her right upper extremity EMG/NCV clearly shows a brachial plexopathy. Physical therapy (including the use of a TENS unit), pharmacotherapy, sympathetic nerve blocks, and biofeedback have shown minimal, if any, benefit. Acupuncture has provided short-term benefit but the effects wane after each treatment.

1. What would you do next for this patient?
  - A. Consider spinal stimulation
  - B. Inform the patient that nothing more can be done
  - C. Encourage the patient to continue acupuncture, explaining that it is likely to benefit her on a long-term basis

- D. Perform a radiofrequency sympathectomy
- E. None of the above

2. Should any of the following "advanced" therapies be considered for this patient?

- A. Intravenous lidocaine infusions
- B. Intravenous saline infusions
- C. Botulinum toxin type A injections
- D. A and C
- E. None of the above

### SEE PAGE 14 FOR ANSWERS AND COMMENTS

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## 10-Minute Office Visit

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important to measure pain, but a pain score alone is not enough to evaluate successful treatment.

**Activities of daily living.** At the initial and each subsequent visit, functional outcome that is meaningful to the patient is discussed and recorded: hobbies, work activities, household duties, social events, exercise targets. Treating any chronic condition requires a return visit to evaluate efficacy.

**Adverse events.** Is the treatment producing a side effect that is unacceptable? Mrs Smith could not tolerate effective treatment because of constipation. Anticipating and requesting side effect information allows for adverse event management rather than discarding effective pain treatment. Patients, especially the elderly, will often accept higher pain levels in order to avoid side effects. With adverse events management, pain levels are controlled with all the accompanying quality of life improvements.

**Aberrant behavior.** If treatment involves an opioid analgesic, most PCPs worry about addiction. At the same time, patients on long-term opioid therapy often display behaviors that make us concerned: early refills, demands for more medication, lost medication, or using the medication with other psychoactive drugs like alco-

hol. Does this behavior indicate addiction, or is it just lost medication or a little social drinking? Sometimes it is difficult to evaluate. The best practice is to document the behavior in the chart, discuss it with the patient, then come up with a mutually agreeable action if the behavior recurs. Often, especially with early refill requests, you may want to just refill the medication again because it is easy and does not require a confrontation. Doing what is easy now may lead to repeat requests and a more difficult confrontation in the future.

For example: you have discussed early refills with a patient who agrees to be more careful around the daughter who "borrows" the patient's pills to treat menstrual cramps. The refill request is a week early again the following month. Document the request for refill and refuse to refill the medication until the appropriate refill interval. This will most assuredly prompt a call from the patient where you explain the agreement about not refilling medication early. The patient complains about withdrawing from the medication and going a week without pain control. You are sympathetic, offer medication to help the withdrawal, but refuse to refill the pain medication. The early refill requests will stop. Documenting this behavior focuses you on setting limits and emphasizing the seriousness of opioid therapy.

Some of the most rewarding and appreciative patients are those who have a sympathetic provider helping them with chronic pain. Yet treating patients with chronic pain is rarely met with enthusiasm in primary care. Patients are complicated, rarely cured, make little progress toward normal life functioning, and often have complex psychosocial issues that you perhaps cannot fully address. There is never enough time to adequately follow up with pain patients yet the PCP is accustomed to dealing with chronic problems. This is accomplished through short, focused visits and a longitudinal experience with patients. After years of knowing a patient, we are familiar with what to expect, when to push, when to give in. We want all our smokers to stop, our morbidly obese to lose weight, our diabetics to check their sugar 3 times a day, but patients do not always do what we want. We do not give up on the noncompliant patient, but keep pressing the issues. The smoker returning from a hospitalization for pneumonia may listen to our smoking lecture. Many pain patients will have a time when exercise and pacing and medication reduction can be discussed. Having a focused plan allows for a 10-minute office visit and directs you and the patient toward the treatment success you both desire. ☞

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## Chronic Pain Is a Disease

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align their efforts and care in productive steps and also provides measurable objectives for improvement while monitoring progress (similar to achieving desired levels of blood sugar or cholesterol for a diabetic patient). Physicians and their patients can and should feel good about sharing short-term successes. Identified accomplishments can then be incorporated into plans for continued, step-wise improvement and can build a focus on well-being and quality of life rather than pain and functional decline.

**Level of psychological pain and morbidity** Patients with chronic pain tend to have increased levels of anxiety, depression, and anger that affect daily functioning. Although these emotional disturbances are common in this setting, they contribute to frustration, a loss of motivation, decreased function, difficulties with interpersonal interactions, and may even precipitate and exacerbate pain. Evaluation, medication, and therapy for significant emotional distress may be necessary to help the patient envision improvement in pain and function.

**Socioeconomic consequences** There are a myriad of potential socioeconomic effects

of chronic pain because of disability, lost workdays, and healthcare expenses. These effects may be especially severe if disability or medical insurance is lacking. While it may be beyond the scope of many physicians to handle these financial issues, it is important to be aware of the significant effect that financial concerns may have on a patient's life and health. Assisting patients through the use of social work referral, compassionate medication programs, medical assistance, and assessment/evaluation for medical disability can be meaningful in helping patients cope with their circumstances and supporting their ability to improve quality of life.

**Social consequences** Patients with chronic pain who have limited mobility tend to feel and become isolated. In addition, anger and psychological morbidity may strain marital, family, and other personal relationships, further increasing psychological distress. This potentially destructive cycle may severely compromise treatment and its success. Recognizing such consequences, identifying potential support, providing counseling, and helping patients overcome isolation may provide great benefit by allowing other aspects of care to progress.

Clearly, the integrated effects of chronic pain on a patient's well-being

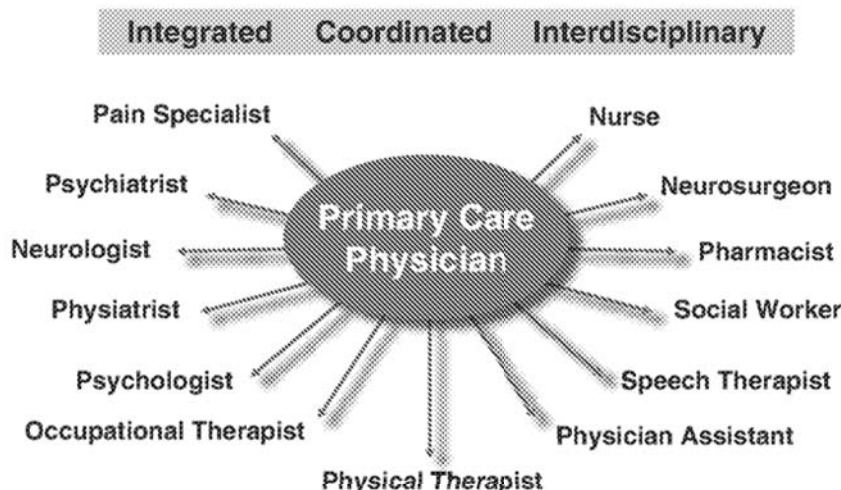
(see Figure 1), in addition to the pain itself, can be detrimental to improvement and success. A major part of the challenge in caring for such patients is dealing with these wide-ranging issues.

*Patients can become invested in their successes, care programs, management, improved self-esteem, and quality of life.*

However, if these issues are recognized and addressed with a multifaceted approach, there is a great potential to improve life situations and enhance positive outcomes of care. In turn, patients can become invested in their successes, care programs, management, and improved self-esteem and quality of life, rather than feeling confined to the difficult circumstances of unalleviated pain.

Finally, it is critical to recognize that the PCP may choose to incorporate a variety of interdisciplinary healthcare professionals (see Figure 2) in evaluating and addressing the complex care and needs of patients. By setting reasonable goals, monitoring progress, using appropriate referral, coordinating care, and/or building an integrated team approach, the potential for success may be increased and the challenge of caring for patients with chronic pain may be lessened.  $\llcorner$

**Figure 2. Primary Care Physician Coordination of the Multidisciplinary Team**



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# Clinical Insights® in Pain Management

## Evidence-Based Algorithm for Neuropathic Pain

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**N**europathic pain is a common type of pain resulting from peripheral or central nervous system pathology. Patients often complain of hypersensitivity to noxious and even non-noxious stimuli in the affected area, and pain may paradoxically be perceived in a denervated area. Treating neuropathic pain is a challenge, and no single therapy has been shown to be consistently effective for all neuropathic pain states. Given the number of treatments that potentially may be used for neuropathic pain, Finnerup and colleagues felt that there was a need for a treatment algorithm.

These investigators recently reviewed the results of over a hundred clinical trials involving neuropathic pain to develop a treatment algorithm. A total of 105 full reports of randomized, placebo-controlled, double-blind studies published in peer-reviewed journals were identified using free-text searches of MEDLINE (1966-April 2005), EMBASE (1974-April 2005), Cochrane Review, and Cochrane CENTRAL. To be considered for this analysis, studies were required to have included at least 10 patients. Among the identified trials, 26 examined antidepressants, 39 anticonvulsants, 11 opioids, 11 capsaicin, 7 N-methyl-D-aspartate (NMDA) receptor antagonists, 9 mexiletine, 4 topical lidocaine, 3 cannabinoids, and 1 a glycine antagonist.

Because studies directly comparing drugs for neuropathic pain were limited, this analysis employed an alternative approach that estimated the relative efficacy and safety using numbers needed to treat (NNT) and numbers needed to harm (NNH). NNT was defined as the number of patients needed to treat with a certain medica-

tion to achieve a defined degree of pain relief (50% pain relief) in one patient, and was calculated by the reciprocal of the absolute risk difference. NNH was defined as the number of patients that needed to be treated for a single patient to drop out because of adverse effects.

This review revealed that tricyclic antidepressants (TCAs) and the anticonvulsants gabapentin and pregabalin were the most frequently studied medications for neuropathic pain. In peripheral neuropathic pain, the lowest NNT was for TCAs (ranging from 2 to 3), followed by valproate, carbamazepine/lamotrigine/phenytoin, opioids, tramadol, and gabapentin/pregabalin. Data on the pharmacologic treatment of central neuropathic pain were limited.

Based on these findings, the authors proposed a pharmacologic treatment algorithm for peripheral neuropathic pain (painful neuropathy, painful diabetic neuropathy, postherpetic neuralgia, and peripheral nerve injury pain) (see Figure). The authors suggested that if postherpetic neuralgia and focal neuropathy are present, the lidocaine patch should be considered. If postherpetic neuralgia and focal neuropathy are not present, a TCA or gabapentin/pregabalin should be considered. The investigators stressed that the potentially dangerous side effects of TCAs and strong opioids should be taken into account when making clinical decisions.

The analgesic effects of gabapentin and TCAs have been consistently demonstrated in large trials, and both might be considered first-line treatment of peripheral neuropathic pain. Because of fewer side effects, serotonin-

norepinephrine reuptake inhibitors (SNRIs) might replace TCAs as more evidence emerges.

Tramadol and oxycodone might be considered second- or third-line medications for neuropathic pain. For tramadol, which contains both an opioid and an SNRI, and the other opioids in the study, the NNT values were low. Furthermore, a direct-comparison study suggested that morphine has an equal, or slightly better, analgesic effect compared with gabapentin. The authors also note that although there is no compelling evidence for problems with dependence and tolerance in the setting of neuropathic pain, such concerns may make opioids a less desirable option.

Combinations of medications with different mechanisms of action might have theoretical justification for neuropathic pain. For instance, in patients with various localized peripheral neuropathic pain syndromes, including the presence of mechanical allodynia, lidocaine patch 5% as add-on therapy has been shown to reduce ongoing pain and allodynia. Except for combinations of gabapentin with venlafaxine or morphine, evidence supporting the use of combination therapy for neuropathic pain is scant.

Carbamazepine has been suggested as first-line therapy for trigeminal neuralgia because of consistent outcomes with a low NNT, although studies supporting its use were of varying quality. Oxcarbazepine might be an alternative for trigeminal neuralgia, although as of yet there are no published trials supporting its use.

Studies exploring treatments for central neuropathic pain are lacking. Therefore, until further studies are



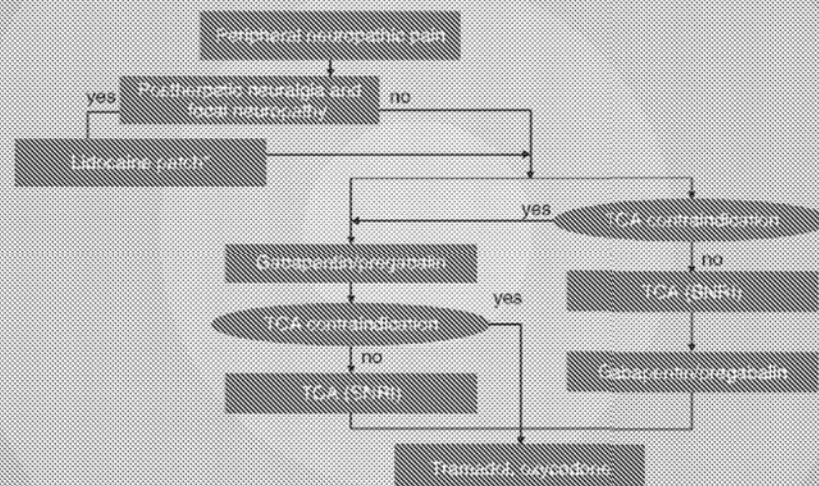
performed, the investigators suggested that a treatment algorithm for central neuropathic pain should be partially based on the experience with peripheral neuropathic pain conditions.

Because TCAs are often not tolerated in elderly patients with stroke, the authors suggested that gabapentin or pregabalin might be appropriate first choices. TCAs, lamotrigine, cannabinoids, tramadol, and opioids are options for second-line therapy.

Although this study examined the available clinical evidence, the authors admitted that the conclusions that can be drawn from this retrospective analysis are limited by the methodological complexity of pooling data from varying studies. ☞

Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain*. 2005;118:289-305.

### Proposed Treatment Algorithm for Peripheral Neuropathic Pain



Reprinted with permission from Finnegan NB et al. *Pain* 2005;118:296.

## COMMENTARY



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Dr Chevlen has indicated that he has no relevant financial relationships to disclose.

The research paper on management of neuropathic pain by Finnerup et al shows both the strengths and the weaknesses of a meta-analysis. Its chief strength is the comprehensive nature of the review. The entire English-language literature of randomized drug trials studying the treatment of neuropathic pain was assessed. The bibliography alone makes this paper worthwhile.

Its chief weakness, however, is the weakness inherent in any meta-analysis. There is simply an almost insurmountable limit as to how much one can conclude from comparisons of different trials. The heterogeneity of the pain states studied, of the drugs, the doses, the durations of the trials,

the tools used to assess pain and adverse effects—all of these factors erode the generalizability of the authors' conclusions.

To their credit, Finnerup et al acknowledge the limitations of meta-analysis, and even give detailed explanation as to the many factors limiting the applicability of their study. Nonetheless, they do not refrain from creating an algorithm that purports to guide clinicians in their approach to patients with neuropathic pain. One example of overreach is their conclusion that cannabinoids may be a reasonable second-choice therapy for neuropathic pain in the elderly. Yet in the merely 3 cannabinoid studies cited, only a handful of

patients were included who were older than 55 years, and none older than 65 years.

The algorithm that the authors develop is indeed based on evidence, but the algorithm itself has not been compared prospectively with other algorithms or with non-algorithmic approaches to treating neuropathic pain. Thus, the algorithm should be viewed as a reasonable first step toward the management of neuropathic pain, one based on extensive clinical experience. However, it should not be mistaken for an indisputable approach to patient care, or as a substitute for the individualized approach that is always the hallmark of good clinical medicine. ☞



## New Delivery Systems

CONTINUED FROM PAGE 4

medication such as fentanyl to control moderate to severe pain.<sup>12</sup> Prospective observational studies have demonstrated that sustained-release transdermal fentanyl in matrix or reservoir formulations are well tolerated and effective for the treatment of moderate to severe chronic pain.<sup>13</sup> In one study, participants with moderate to severe chronic pain preferred transdermal fentanyl over sustained-released morphine because of less constipation, better pain relief, and thus enhanced quality of life. Disadvantages of transdermal applications of opiates include difficulty with titration due to 12-hour onset of action and 3-day duration of each application.<sup>14</sup> Therefore, patients with stable chronic pain, as opposed to patients with a variable pain pattern, may be best suited for transdermal opiate therapy.

Optimal management of patients with chronic pain requires that pain types (ie, inflammatory, neuropathic, or mixed) and intensity be identified in order to utilize the most effective therapy. Initial assessment and subsequent reassessment at regular intervals will determine whether combination therapy—which may include topicals, nonsteroidal anti-inflammatory drugs, antidepressants, anticonvulsants, and

opiate medications—is indicated. When considering opiate therapy, each patient must be evaluated regarding efficacy, as well as risk-related issues such as dependency, abuse, and addiction. In the overall pain population, the risks are small but real in everyday clinical practice. Therefore, adoption of a general pain management plan, along with implementation of an ongoing assessment plan for patients with chronic pain who are on chronic opiate therapy, will lead to improved outcomes for both the patient and the clinician.<sup>15</sup> ❧

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### ANSWERS AND COMMENTS FOR CRPS CASE STUDIES (SEE PAGE 5)

#### Patient With CRPS Type I

- Integrated multidisciplinary treatment approaches provide a patient with the best opportunity for a good outcome, although they can be difficult to coordinate. Single treatments may also provide benefit; however, the integrated approach proves the most likely to achieve the best results. (Correct answer is E)
- The patient has been treated with a number of agents with proven benefit and/or FDA approval for neuropathic pain, but has not responded well. Although several of the agents listed are approved to treat one or more neuropathic pain conditions (see Table on page 4), there is currently no pharmacological agent that is specifically FDA-approved for CRPS. Thus, these agents are used most often in an "off-label" manner. Lamotrigine has been shown to be effective for neuropathic pain associated with diabetic polyneuropathy as well as for HIV polyneuropathy. Opioids, specifically long-acting,

have been shown to be helpful in the treatment of neuropathic pain as well. Based on this patient's presentation, an optimal regimen may include the use of two or more agents with differing mechanisms of action. (Correct answer is E)

#### Patient With CRPS Type II

- Spinal stimulation can be extremely helpful for patients with neuropathic pain, including CRPS. The biggest advantage of this intervention is that it is reversible—if a trial of stimulation is not helpful, no permanent damage is likely to have been experienced. Even if the pain relief is not as robust after several years (as recently reported\*), for this patient, who is refractory to other less invasive treatments, spinal stimulation may provide sufficient pain relief to be beneficial from a functional recovery viewpoint. Regrettably, long-term benefit has not been established for many of the pain interventions commonly used. However, there is a 25% chance of increasing the pain when a sympathectomy is performed, and whether this increase is permanent or not cannot be predicted. While no study has shown

acupuncture to be successful in providing long-term relief in CRPS, anecdotal experiences suggest that some patients do report pain relief with this modality. (Correct answer is A)

- There is increasing evidence for the use of intravenous lidocaine infusions to treat a number of neuropathic pain states. The potential use of botulinum toxin type A in the treatment of trigeminal neuralgia, postherpetic neuralgia, spinal cord injury pain, and CRPS type I has been suggested in several small studies. Since the mechanism of action of botulinum toxin type A may include inhibition of the release of glutamate, substance P, as well as calcitonin gene-related peptide (CGRP), there is at least a theoretical basis for the observed analgesic effect in these neuropathic pain states. Further study is currently underway. (Correct answer is D)

\*Kemler MA, de Vet HCW. Spinal cord stimulation for chronic reflex sympathetic dystrophy—five-year follow-up [correspondence]. *N Engl J Med.* 2006;354:2394-2396.



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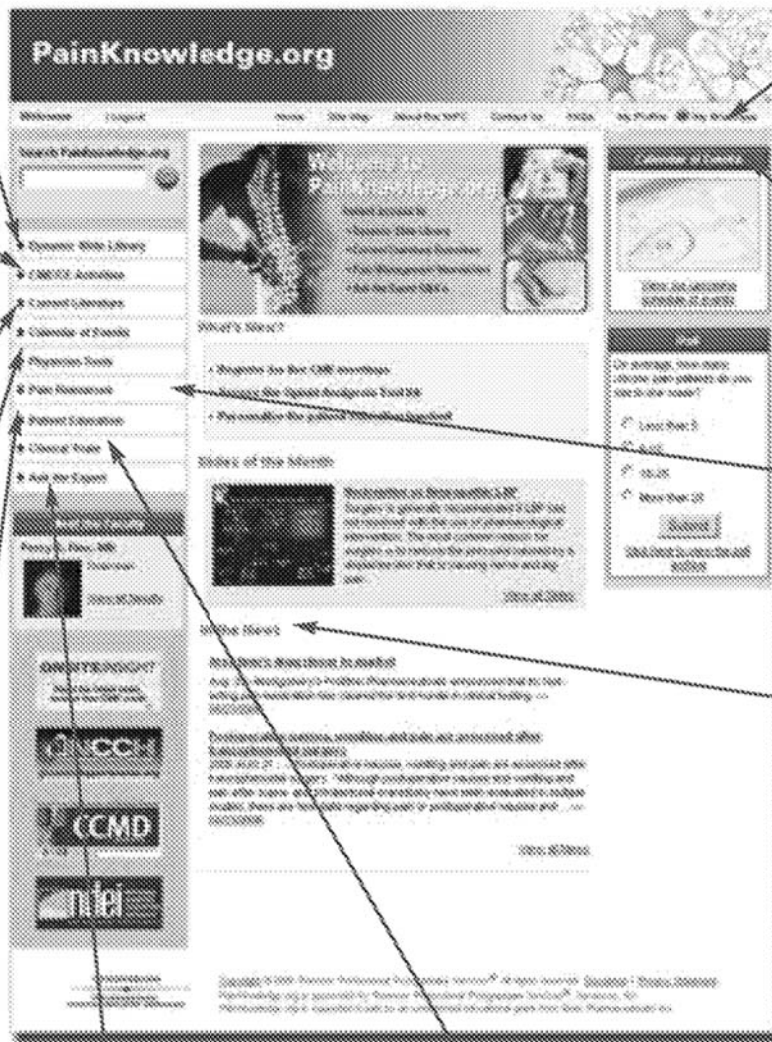
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